view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Applicants note that the Examiner has acknowledged Applicants' election of Group I with traverse in Paper 16 (8/7/02) and in Paper 18 (10/29/02).

1-3. Applicants note with appreciation that the amendments put forth in Paper 6 and Paper 16 have been entered in full.

Claims 1-2, 4, and 6-32 are pending claims in the present application. Applicants note that claims 3, 19-20, 22-28, and 30 are withdrawn from consideration as being drawn to a non-elected invention, and claims 1-2, 4-18, 21, and 29 were elected with traverse. Applicants will cancel non-elected claims upon indication of allowable subject matter.

4. The drawings are objected to as set forth in the PTO-948. In reply to the Office Action, Applicants submit corrected drawings herewith. Accordingly, reconsideration and withdrawal of this rejection is requested.

5-6. Claims 1-2, 4-18, 21, and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. To expedite prosecution, Applicants have amended the claims to incorporate the Examiner's suggestions. Such amendments are not made in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

a. Applicants have amended claim 1 by changing the phrase "a *hedgehog* or *ptc* therapeutic" to "a *hedgehog* agonist or antagonist" to obviate the rejection. Because this change is based on the definition of *hedgehog* therapeutic in the specification, Applicants submit that this change does not narrow the scope of this claim.

b. Applicants contend that the term "modulating" is described in detail in the specification such that one of skill in the art would readily recognize that this term encompasses both enhancing and suppressing immune function (see, e.g., page 2, lines 6-10; page 6, lines 19-22; page 9, line 16). Nevertheless, to expedite prosecution, Applicants have amended claim 1 to

clarify the subject matter being claimed. Applicants further point out that claim 1 is a generic claim linking the elected Group I and the non-elected Group II.

c. Applicants contend that the term "*hedgehog* polypeptide" was well known in the art at the time of filing, and is described in detail in the specification such that one of skill in the art would readily recognize the metes and bounds of the claimed subject matter. Nevertheless, to expedite prosecution, Applicants have amended the claims to define the claimed *hedgehog* polypeptides with respect to the disclosed sequences.

d. Applicants contend that the term "effective amount" is defined in the specification (page 7, lines 7-11) such that one of skill in the art would recognize the metes and bounds of the claimed subject matter. Nevertheless, to expedite prosecution, Applicants have amended the claims as suggested by the Examiner.

e. Applicants' amendment of the term 'homology' obviates the rejection.

f. Applicants contend that the term "stringent conditions" is art-recognized. The claims recite the term "stringent" to characterize the hybridization conditions. In the parlance of the molecular biologist the composite term "stringent (hybridization) conditions" has come to signify those conditions of heat and salt which are standard for the detection of genes in mammals using a hybridization-dependent detection method such as a Southern Hybridization (see, e.g., pp. 9.47-9.57 of Sambrook, Fritsch and Maniatis (1989) Molecular Cloning, 2nd ed., Cold Spring Harbor Press). Thus, to one of skill in the art, the expression "stringent" is not ambiguous. Nevertheless, to expedite prosecution, Applicants have amended claim 7 to explicitly specify the stringency conditions.

In view of the above amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw all rejections under 35 U.S.C. 112, second paragraph.

7-8. Claims 1-2, 4-18, 21, and 29 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicants traverse this rejection to the extent that it is maintained over the amended claims.

The Examiner acknowledges that Applicants have enabled "for methods of suppressing or promoting thymic T-cell maturation comprising administering a polypeptide at least 80% identical to the N-terminal autoproteolytic fragment of a sonic hedgehog polypeptide, wherein said peptide binds a naturally occurring patched protein." However, the Examiner further asserts that Applicants have failed to provide enablement for the broad scope of suppressing or enhancing the immune function or immune system of an animal, nor for modulating T-cell maturation other than in the thymus, nor for any form of therapy, and nor for the suppression of promotion of T-cell maturation comprising the administration of a hedgehog or ptc therapeutic or agonist thereof other than a polypeptide at least 80% identical to the N-terminal autoproteolytic fragment of a sonic hedgehog polypeptide.

Applicants point out that in accordance with MPEP 2164.02, "[a]n example may be either working or prophetic. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved." As pointed out by the Examiner, Applicants have provided working examples demonstrating the efficacy of *hedgehog* agonists or antagonists in suppressing or promoting (respectively) thymic T-cell maturation in vitro. Applicants have also disclosed prophetic examples demonstrating the vivo application of the claimed methods (see, e.g., page 9-12). These prophetic examples can be easily evaluated based on the methods disclosed by Applicants, and are sufficient to meet the requirement of 35 U.S.C. §112, first paragraph, that one of ordinary skill be taught how to use the invention. Given the teachings of the present application, the efficacy of *hedgehog* agonists or antagonists in suppressing or promoting thymic T-cell maturation both in vivo and in vitro can be readily evaluated without undue experimentation. This is the standard under MPEP 2164.08(b), which states that "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art."

Applicants have successfully demonstrated the efficacy of the invention in suppressing or promoting thymic T-cell maturation by utilizing a model system of thymic organ culture. This demonstrates that the claimed methods are at least enabled for suppressing or promoting thymic T-cell maturation under in vivo and/or ex vivo conditions. Applicants cannot be expected to test

the claimed methods in every step of immune function/system. This sentiment was echoed by the Federal Circuit in *In re Brana*. In addressing whether the invention satisfied the utility requirement, the Court found that the applicants' experimental evidence in a particular tumor model was sufficient evidence of the utility of the invention. Furthermore, it is well known in the art that T cell maturation in the thymus is not only a critical step in T cell development, but also essential for an individual to acquire full immune function/system. Thus, there is no reason for one skilled in the art to doubt that immune function/system can be modulated by suppressing or enhancing T cell maturation, as claimed in the present invention. Applicants remind the Examiner that "[I]n order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention" (MPEP 2164.04). Applicants further point out that "[I]f reasonably correlated to the particular therapeutic or pharmacological utility, data generated using in vitro assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process" (MPEP 2107.03). Accordingly, Applicants submit that, absent evidence that immune function as a whole is not affected by the claimed methods, the methods employed by Applicants are representative of the broad scope of suppressing or enhancing the immune function/system of an animal.

The Examiner has cited one reference to support his position that one of skill in the art would have reasonable basis to presume that *hedgehog* agonists or antagonists would not function as disclosed by Applicants (Lowrey et al., 2002, which was listed as Lowery et al., 1999 in the Office Action). Specifically, the Examiner argues that "Lowrey et al. report that sonic hedgehog promotes, rather than inhibits, cell cycle progression in activated peripheral CD4+ T cells, an effect opposite to that of the instantly reported effect on T cell maturation in the thymus." Applicants remind the Examiner that the determination of enablement must be made based on an evaluation of the evidence as a whole (MPEP 2164.05). The consideration of this reference over the evidence presented by both Applicants and by others in the art constitutes unfair picking and choosing of references. Lowrey et al. utilized cultured CD4+ T cells isolated from mice spleens to study clonal expansion of peripheral CD4+ T cells. Clealy, Applicants and Lowrey et al. employed different model systems and investigated different aspects of T cell development, which makes this particular reference irrelevant to the claimed subject matter. Further, the results of Lowrey et al. are not internally consistent as to the stimulatory effect of

sonic hedgehog (Shh) on T cell proliferation. For example, Lowrey et al. observed that exogenous Shh increased CD4+ T cell proliferation significantly merely in response to suboptimal stimulation with anti-CD3/28 antibodies. Indeed, Lowrey et al. acknowledged that "exogenous Shh failed to amplify T cell proliferation induced by optimal doses of anti-CD3/28 antibodies" (page 1873, column 2; and figure 3D). Thus, given the results from Lowrey et al., one skilled in the art would not be convinced that Shh promotes cell cycle progression in activated T cells.

The Examiner has cited another reference to argue that a highly skilled artisan could not determine what a "therapeutic amount" of sonic hedgehog is, as it relates to immune function (Budec et al., 1996, which was listed as Dubec et al., 1996 in the Office Action). Applicants remind the Examiner again that the determination of enablement must be made based on an evaluation of the evidence as a whole (MPEP 2164.05). The Examiner takes the stand that ethanol is known in the art to inhibit the CD4-CD8 double negative/double positive transition in vivo, yet ethanol is not used in immune therapy. Assuming this is true, one skilled in the art would understand that ethanol is clearly distinguishable from hedgehog agonists in many other biological effects, which may explain why ethanol is not used in immune therapy. For example, ethanol does not have a specific receptor, and exerts non-specific and pleotropic effects in the body. As a result, the use of ethanol is associated with a wide range of familiar and undesirable side-effects that limit its therapeutic use as an immune suppressor. In contrast, hedgehog agonists act through the patched receptor and elicit specific signaling activities. Thus, whether or not ethanol is used in immune therapy is not relevant to the enablement of the claimed subject matter. In addition, according to MPEP 2107.03(V), issues such as drug safety and efficacy are not a proper concern of the Patent Office. "The Office must confine its review of patent applications to the statutory requirements of the patent law. ... [I]t is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the *degree* of effectiveness. [citations omitted]" (emphasis original) Further, in reply to the Examiner's objection to the "therapeutic amount," Applicants submit that, according to MPEP 2164.01, "it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation." As amended, claims 1-2 and 31 recite an "effective" amount, which varies somewhat from patient to patient based on many different factors . Nevertheless, a skilled artisan can readily determine an effective amount

for a particular patient without undue experimentation once information on the relevant factors is known, or even just by beginning with a subtherapeutic dose and increasing the dosage until the desired response is obtained.

The Examiner further alleges that "the specification has provided results with the administration of the N-terminal autoproteolytic fragment of a sonic hedgehog polypeptide or an anti-hedgehog antibody, such fragment being known to bind patched protein, yet the claims comprise an essentially unlimited genus of proteins that would not be expected to bind mammalian patched." Thus, the claims are additionally rejected for allegedly failing to enable treatment with agonists or antagonists other than a polypeptide. Applicants maintain that the *hedgehog* signaling pathway is presented in detail in the specification (page 46, line 14 - page 47, line 3), and furthermore that this pathway was well known in the art at the time of filing. Applicants have additionally provided a detailed description of small molecule *hedgehog* agonists or antagonists including inhibitors of PKA (page 48, line 24 - page 50, line 10). Furthermore, Applicants provide high-throughput screens that could be used to identify other small molecule *hedgehog* agonists or antagonists. Applicants have provided a detailed definition of *hedgehog* agonists or antagonists, and the functional characteristics that exemplary *hedgehog* agonists or antagonists would possess. These functional characteristics would allow one of skill in the art to identify small molecule agonists or antagonists without undue experimentation.

The Examiner has cited Stull and Iacovitti to argue that the details of *hedgehog* signaling are still unpredictable (Stull and Iacovitti, 2001). Applicants contend that this reference is not applicable to the present invention. Stull and Iacovitti analyze the ability of Shh to augment or alter the effects of various FGFs on neural cultures. None of the experiments of Stull and Iacovitti examine the effects of Shh administered in the absence of FGFs. Therefore, it is impossible to evaluate the effects of agonizing *hedgehog* signaling in this system because *hedgehog* signaling is never examined. All that can reasonably be inferred from these experiments is that some ill-defined interaction between hyperactivation of FGF signaling and *hedgehog* protein may inhibit *hedgehog* signaling. Applicants' invention requires agonizing or antagonizing *hedgehog* signaling. Since this approach was never addressed by Stull and Iacovitti, it is logically unsound to attempt to reconcile their conclusions with Applicants' data. Moreover,

Applicants need not explain or describe *why* the invention works; it is sufficient to show that it does.

The Examiner has also cited Bryce et al. to argue that the relationship between PKA and the activity of T cells is complex and unpredictable (Bryce et al., 1999). Applicants contend that this reference is not applicable to the present invention. As described in the specification (page 48, lines 27-32), Applicants note that high PKA activity has been shown to antagonize hedgehog signaling, and hypothesize that hedgehog signaling occurs via inhibition of PKA activity. In contrast, Bryce et al. fail to show whether PKA inhibitors can effect hedgehog signaling in T cells. In addition, all the experiments of Bryce et al. examine the effects of PKA inhibitors administered in the presence of elevated cAMP level, a complication which only further muddies the relevance of the results to the claimed invention. Therefore, given the results from Bryce et al., one skilled in the art would be unable to determine or predict the effect of PKA inhibitors on *hedgehog* signaling because it is never examined.

Applicants contend that the amended claims are enabled throughout their scope. Applicants have presented working examples demonstrating the use of *hedgehog* agonists or antagonists in suppressing or promoting thymic T-cell maturation, respectively. The specification also describes in detail that immune function/system, as a whole, could be modulated (either enhanced or suppressed) by the methods of the invention, as well as other agonists or antagonists that could be used in modulating immune function/system. The efficacy of these prophetic embodiments of the invention can be readily evaluated by one of skill in the art without undue experimentation. Applicants have provided extensive discussion of methods which can be used to evaluate these prophetic embodiments, and the understanding of *hedgehog* signaling in the art is very high. Furthermore, Applicants contend that the references cited by the Examiner asserting the unpredictability of the art with respect to *hedgehog* signaling are not applicable to the claimed invention and should not be considered in the face of the extensive evidence presented by Applicants. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

9. Claims 1, 4-18, and 21 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants traverse this rejection to the extent that it is maintained over the amended claims.

Applicants have amended the claims to more explicitly point out that the claimed therapeutics are *hedgehog* agonists or antagonists. *Hedgehog* agonists are defined as "a *hedgehog* therapeutic which mimics or potentiates the activity of a wild-type *hedgehog* protein" (page 6, lines 22-23). Conversely, *hedgehog* antagonists are defined as "a *hedgehog* therapeutic which inhibits the activity of a wild-type hedgehog protein" (page 6, lines 23-24). Such *hedgehog* agonists and antagonists are described in detail in the specification, which provides both examples and functional characteristics of *hedgehog* agonists and antagonists.

The *hedgehog* pathway is described in detail (page 46, line 14 - page 47, line 3), as are the identified *hedgehog* polypeptides (page 13, line 13 - page 14, line 16). In addition to this detailed general description of the *hedgehog* pathway and *hedgehog* polypeptides, Applicant specifically described the *hedgehog* polypeptides of the invention (page 2, lines 17-23): "[T]he hedgehog protein has an amino acid sequence at least 60, 75, 85, or 95 percent identical with a *hedgehog* protein of any of SEQ ID Nos. 10-18 or 20, though sequences identical to those sequence listing entries are also contemplated as useful in the present method. The *hedgehog* protein can be encoded by a nucleic acid which hybridizes under stringent conditions to a nucleic acid sequence of any of SEQ ID Nos. 1-9 or 19, e.g., the *hedgehog* portion can be encoded by a vertebrate *hedgehog* gene, especially a human *hedgehog* gene."

One of skill in the art would have been able to recognize which compounds are *hedgehog* agonists or antagonists because Applicants defined a *hedgehog* agonist or a *hedgehog* antagonist as described above. Furthermore, contrary to what the Office Action alleges, Applicants have demonstrated possession of the claimed invention by describing examples of actual reduction to practice of structurally diverse compounds. At least one hedgehog agonist (e.g., an octyl-modified Shh) and one hedgehog antagonist (e.g., an anti-hedgehog antibody) are described in the working example. Moreover, there is no reason to doubt that the other compounds asserted in the application to agonize or antagonize hedgehog activity, compounds already well known in the art, would fail to act analogously in the presently claimed methods.

The *hedgehog* agonists or antagonists of the invention also include small organic molecules. Applicants have provided a detailed description of one class of exemplary small molecules: PKA inhibitors (page 48, line 24 - page 50, line 10). Additionally, Applicants provide a detailed discussion of high-throughput screens which could easily identify additional small molecules (page 41, lines 12-31). Such high-throughput screens were well known in the art at the time of filing, and one of skill in the art could easily identify, without undue experimentation, small molecule *hedgehog* agonists or antagonists which would fulfill the criteria enumerated in the disclosure.

In summary, the terms *hedgehog* agonist and antagonist are described in detail throughout the specification such that one of skill in the art could easily envision the polypeptides and small molecules of the invention. Such compounds must fulfill the functional criteria of activating/stimulating or inhibiting/suppressing *hedgehog* signaling respectively. A representative number of such compounds are enumerated in the application, as well. Applicants have even provided several experimental measures that would allow one of skill in the art to readily recognize the claimed subject matter. For the reasons presented above, Applicants submit that all pending claims as amended fully comply with the written description requirement. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. 112, first paragraph, is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims as amended are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby

petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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